Modifiers of the effect of maternal multiple micronutrient supplementation on stillbirth, birth outcomes, and infant mortality: a meta-analysis of individual patient data from 17 randomised trials in low-income and middle-income countries

Emily R Smith, Anuraj H Shankar, Lee S-F Wu, Said Aboud, Seth Adu-Afarwuah, Hasmot Ali, Rina Agustina, Shams Arifeen, Per Ashorn, Zulfiqar A Bhutta, Parul Christian, Delanjathan Devakumar, Kathryn G Dewey, Henrik Friis, Exnevia Gomo, Piyush Gupta, Pernille Kæstel, Patrick Kolsteren, Hermann Lanou, Kenneth Maleta, Aissa Mamadoultaibou, Gernard Msamanga, David Osrin, Lars-Åke Persson, Usha Ramakrishnan, Juan A Rivera, Arjumand Rizvi, H P S Sachdev, Willy Urassa, Keith P West Jr, Noel Zagre, Lingxia Zeng, Zhonghai Zhu, Wafaie W Fawzi, Christopher R Sudfeld

Summary

Background Micronutrient deficiencies are common among women in low-income and middle-income countries. Data from randomised trials suggest that maternal multiple micronutrient supplementation decreases the risk of low birthweight and potentially improves other infant health outcomes. However, heterogeneity across studies suggests influence from effect modifiers. We aimed to identify individual-level modifiers of the effect of multiple micronutrient supplements on stillbirth, birth outcomes, and infant mortality in low-income and middle-income countries.

Methods This two-stage meta-analysis of individual patient included data from 17 randomised controlled trials done in 14 low-income and middle-income countries, which compared multiple micronutrient supplements containing iron-folic acid versus iron-folic acid alone in 112 953 pregnant women. We generated study-specific estimates and pooled subgroup estimates using fixed-effects models and assessed heterogeneity between subgroups with the χ^2 test for heterogeneity. We did sensitivity analyses using random-effects models, stratifying by iron-folic acid dose, and exploring individual study effect.

Findings Multiple micronutrient supplements containing iron-folic acid provided significantly greater reductions in neonatal mortality for female neonates compared with male neonates than did iron-folic acid supplementation alone (RR 0·85, 95% CI 0·75–0·96 *vs* 1·06, 0·95–1·17; p value for interaction 0·007). Multiple micronutrient supplements resulted in greater reductions in low birthweight (RR 0·81, 95% CI 0·74–0·89; p value for interaction 0·049), small-for-gestational-age births (0·92, 0·87–0·97; p=0·03), and 6-month mortality (0·71, 0·60–0·86; p=0·04) in anaemic pregnant women (haemoglobin <110g/L) as compared with non-anaemic pregnant women. Multiple micronutrient supplements also had a greater effect on preterm births among underweight pregnant women (BMI <18·5 kg/m²; RR 0·84, 95% CI 0·78–0·91; p=0·01). Initiation of multiple micronutrient supplements before 20 weeks gestation provided greater reductions in preterm birth (RR 0·89, 95% CI 0·85–0·93; p=0·03). Generally, the survival and birth outcome effects of multiple micronutrient supplementation were greater with high adherence (≥95%) to supplementation. Multiple micronutrient supplements did not significantly increase the risk of stillbirth or neonatal, 6-month, or infant mortality, neither overall or in any of the 26 examined subgroups.

Interpretation Antenatal multiple micronutrient supplements improved survival for female neonates and provided greater birth-outcome benefits for infants born to undernourished and anaemic pregnant women. Early initiation in pregnancy and high adherence to multiple micronutrient supplements also provided greater overall benefits. Studies should now aim to elucidate the mechanisms accounting for differences in the effect of antenatal multiple micronutrient supplements on infant health by maternal nutrition status and sex.

Funding None.

Lancet Glob Health 2017; 5: e1090–100

See **Comment** page e1050

Department of Global Health and Population (E R Smith ScD, W W Fawzi DrPH, C R Sudfeld ScD), **Department of Nutrition** (A H Shankar ScD), **Harvard T.H. Chan School of Public Health, Boston, MA, USA; Division of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital, Boston, MA, USA** (E R Smith); **Summit Institute of Development, Mataram, Indonesia** (A H Shankar, R Agustina PhD); **The JiVitA Project, Johns Hopkins University in Bangladesh, Gaibandha, Bangladesh** (L S-F Wu MHS, H Ali MPH, P Christian DrPH, K P West Jr DrPH); **Center for Human Nutrition, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA** (L S-F Wu, H Ali, P Christian, K P West Jr); **Department of Microbiology and Immunology, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania** (S Aboud PhD, W Urassa PhD); **Department of Nutrition and Food Science, University of Ghana, Legon, Accra, Ghana** (S Adu-Afarwuah PhD); **Department of Nutrition, Faculty of Medicine, Universitas Indonesia – Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia** (R Agustina); **International Centre for Diarrhoeal Diseases Research Bangladesh (ICDDR,B), Dhaka,**

Introduction

Micronutrient deficiencies are common among women in low-income and middle-income countries mainly due to inadequate dietary intake and limited diversity of fruits, vegetables, animal protein, and fortified foods.[1] The burden and severity of micronutrient deficiencies are exacerbated during pregnancy because of increased demands of both the mother and the growing fetus.[2] It is

Bangladesh (S Arifeen DrPH); **Centre for Child Health Research and Department of Paediatrics, University of Tampere School of Medicine and Tampere University Hospital, Tampere, Finland** (P Ashorn PhD); **Center for Global Child Health, Hospital for Sick Children, Toronto, ON, Canada** (Z A Bhutta PhD); **Center of Excellence in Women and Child Health, The Aga Khan University, Karachi, Pakistan** (Z A Bhutta, A Rizvi MSC); **UCL Institute for Global Health, London, UK** (D Devakumar PhD, D Osrin PhD); **Department of Nutrition and Program in International and Community Nutrition, University of California-Davis, Davis, CA, USA** (K G Dewey PhD); **Department of Nutrition Exercise and Sports, University of Copenhagen, Copenhagen, Denmark** (H Friis PhD, P Kæstel PhD); **College of Health Sciences, University of Zimbabwe, Harare, Zimbabwe** (E Gomo PhD); **Department of Pediatrics, University College of Medical Sciences, Delhi, India** (P Gupta MD); **Nutrition and Child Health Unit, Department of Public Health, Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium** (P Kolsteren PhD); **Faculty of Bio-science engineering, Ghent University, Belgium** (P Kolsteren); **Institut de Recherche en Sciences de la Santé, Ministry of Scientific Research and Innovation, Ouagadougou, Burkina Faso** (H Lanou MD); **School of Public Health and Family Medicine, University of Malawi College of Medicine, Blantyre, Malawi** (K Maleta PhD); **Food and Agriculture Organization of the United Nations, Libreville, Gabon** (A Mamadoultaibou MS); **Department of Community Health, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania** (G Msamanga ScD); **Department of Women's and Children's Health, International Maternal and Child Health, Uppsala University, Uppsala, Sweden** (L-Å Persson PhD); **Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, USA** (U Ramakrishnan PhD); **Instituto Nacional de Salud Publica, Cuernavaca, Mexico** (J A Rivera PhD); **Pediatric and**

Research in context

Evidence before this study

Micronutrient deficiencies are common in pregnant women in low-income and middle-income countries. However, debate persists regarding the current WHO recommendation to provide pregnant women with iron-folic acid supplementation alone, rather than multiple micronutrient supplements containing other essential micronutrients in addition to iron-folic acid during routine antenatal care. In the past two decades, more than 20 randomised trials have examined the effect of multiple micronutrient supplements during pregnancy, compared with iron-folic acid alone, on maternal and child health outcomes. The 2017 Cochrane review and meta-analysis established that provision of daily oral multiple micronutrient supplements reduced the risk of low birthweight (<2500 g) and small-for-gestational-age births, but had no overall effect on perinatal and neonatal mortality as compared with iron-folic acid alone.

The recently updated 2016 WHO antenatal care recommendations acknowledged that policy makers in populations with a high prevalence of maternal nutritional deficiencies might wish to provide multiple micronutrient supplements. However, WHO does not universally recommend multiple micronutrient supplements, noting: "There is some evidence of additional benefit of multiple micronutrient supplements containing 13–15 different micronutrients (including iron and folic acid) over iron and folic acid supplements alone, but there is also some evidence of risk, and some important gaps in the evidence".

Added value of this study

This study uses the most detailed approach to analysing existing trial data on multiple micronutrient supplements. Previous meta-analyses identified overall benefits of multiple micronutrient supplements in terms of birth size, but our findings show that specific subgroups experience mortality benefits, notably female neonates. Women with indicators of malnutrition during pregnancy who took multiple micronutrient supplements also had greater reductions in low birthweight, preterm, and small-for-gestational-age births. We found no evidence that multiple micronutrient supplements significantly increased the risk of stillbirth or neonatal, 6-month, or infant mortality, neither overall or in any of the 26 examined subgroups.

Implications of the available evidence

This novel analysis identified subgroups of mothers and infants that might benefit the most from multiple micronutrient supplements. This new evidence suggests that WHO might wish to re-evaluate the balance of benefits and harms of universal multiple micronutrient supplementation in their antenatal care recommendations.

well established that iron-deficiency anaemia in pregnancy can lead to decreased birthweight, and insufficient folate concentrations in the periconceptional period increases the risk of neural tube defects and other adverse outcomes.[3–5] Deficiencies in other micronutrients including vitamins A, B-complex, D, E, zinc, calcium, copper, magnesium, selenium, and iodine are also prevalent in low-income and middle-income countries and can lead to poor pregnancy, fetal growth, and child health outcomes.[3,6–8] As such, maternal multiple micronutrient supplementation including iron-folic acid is a potential intervention to improve maternal and child health as compared with iron-folic acid supplementation alone.

The 2017 Cochrane Systematic Review and meta-analysis that assessed the effect of maternal multiple micronutrient supplements in pregnancy on infant mortality identified 19 randomised controlled trials and pooled data from 17 of these studies.[6] Provision of multiple micronutrient supplements in combination with iron-folic acid during pregnancy reduced the risk of low birthweight (<2500 g; relative risk [RR] 0·88, 95% CI 0·85–0·91) and small-for-gestational-age births (0·92, 0·86–0·98), but had no significant effect on perinatal (1·01, 0·91–1·13) and neonatal mortality (1·06, 0·92–1·22) as compared with iron-folic acid supplementation alone.[6] There was moderate heterogeneity, as measured by I^2, of the effect of multiple micronutrient supplements on some birth outcomes across published trials but substantial heterogeneity for perinatal mortality. A previously published pooled analysis of 12 multiple micronutrient supplements trials also indicated the effect of multiple micronutrient supplements on birthweight may be greater in pregnant women with higher BMI.[9]

In 2016, WHO reviewed their antenatal care recommendations and acknowledged that policy makers in populations with a high prevalence of nutritional deficiencies might wish to provide multiple micronutrient supplements containing iron and folic acid. However, WHO did not universally recommend multiple micronutrient supplements, noting that there was evidence of benefit but also some evidence of harm.[10] The existing data also precluded definitive conclusions if any subgroups experience greater benefits or harm due to multiple micronutrient supplements.

In this study we aimed to elucidate individual-level effect modifiers that might alter the impact of maternal multiple micronutrient supplements on stillbirth, birth outcomes, and infant mortality. We aimed to identify subgroups of pregnant women and infants who might experience greater benefit or harm from multiple micronutrient supplements and explore the sources of the heterogeneity across randomised trials.

Methods

In this two-stage meta-analysis of individual patient data, we identified potential studies for inclusion

through a review of recent meta-analyses.[6,11,12] We then updated this list of potential studies using the search strategy employed by the 2015 Cochrane Review to identify randomised controlled trials published up to July 20, 2015.[6] We also reviewed the references of included trials and systematic reviews; there were no language restrictions.

Eligible studies were randomised controlled trials of multiple micronutrient supplements for pregnant women, containing at least three micronutrients; were done in low-income and middle-income countries as defined by the World Bank; included a control group that had received iron and folic acid supplements as part of the trial or as standard of care; whose authors presented data on birth outcomes, stillbirth, or infant mortality; and whose authors agreed to participate in this new individual patient data study. We excluded trials or trial groups that used lipid-based micronutrient supplements and micronutrient-fortified powders as these provided additional calories and nutrients that might have independent effects on outcomes of interest.

All outcomes, subgroups, and statistical methods were defined a priori. Outcomes of interest included: stillbirth, early neonatal (≤7 days age), neonatal (≤28 days age), 6-month (≤180 days age), and infant (≤365 days age) mortality. Birth outcomes included: birthweight, very low birthweight (<2000 g), low birthweight (<2500 g), early preterm (<34 weeks gestation), preterm (<37 weeks gestation), small-for-gestational-age (<10th percentile of weight-for-gestational-age and sex as defined by Oken[13] and Intergrowth[14] standards), and large-for-gestational-age (>90th percentile as defined by Oken[13] and Intergrowth[14] standards). Births that occurred before 33 weeks or after week 43 were excluded from Intergrowth[14] analyses because small-for-gestational-age and large-for-gestational-age cutoffs were not defined for these gestational ages at the time of analysis.

We assessed the effect of multiple micronutrient supplements on all outcomes within the following subgroups selected based on biological plausibility and inclusion in previous meta-analyses: gestational age at randomisation (trimesters and <20 weeks *vs* ≥20 weeks), parity (1 child *vs* ≥2 children), maternal age (<18 years *vs* ≥18 years and <20 years *vs* ≥20 years), maternal underweight at randomisation (BMI <18·5 kg/m² *vs* ≥18·5 kg/m²), maternal anaemia at randomisation (<110 g/L *vs* ≥110 g/L), maternal stature (<150 cm *vs* ≥150 cm), maternal education (none *vs* ≥1 year), infant sex (male *vs* female), and adherence to trial regimen (≥95% *vs* <95%). We examined the effect of multiple micronutrient supplements on stillbirth and mortality outcomes by the presence of a skilled birth attendant at delivery (yes *vs* no).

We contacted principal investigators of each study and invited them to participate in this study. Eight trials provided individual-level data to the Harvard T.H. Chan investigators (ERS and CRS) and nine independently conducted the subgroup analyses in accordance with the study protocol and using the same statistical analysis code. We calculated non-parametric relative risk or mean difference estimates and corresponding 95% CIs for individually randomised trials. We calculated estimates and 95% CIs for cluster randomised trials using methods consistent with the primary published paper.

We pooled study-specific relative risk and mean difference estimates using fixed effects models using STATA version 14 METAN command. We excluded trials which did not contribute at least one subject to all strata within a subgroup analysis. Heterogeneity within strata was quantified using the I^2 test statistic and corresponding p value, while heterogeneity between subgroups was assessed with the χ^2 test for heterogeneity. We qualitatively assessed study quality using the Child Health Epidemiology Reference Group standards.[15] As a sensitivity analysis for individual subgroup effects, we generated pooled subgroup estimates using random-effects models; we also examined overall and subgroup effects separately for trials using the same dose of iron in the multiple micronutrient supplements and comparison group and again for the trials using a lower dose iron in the multiple micronutrient supplements group than the comparison group. In addition, we did an influence analysis for significant results whereby we presented pooled estimates omitting each study, one at a time (appendix pp 218–220).[16] To assess publication bias and small study effects we visually inspected funnel-plots (appendix pp 221–224). All individual trials were approved by their respective ethics committees. The pooling study protocol was approved by the Harvard T. H. Chan School of Public Health IRB (15-2969).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 19 randomised controlled trials that met our inclusion criteria, 17 of which were included in this meta-analysis.[17–33] Two were not included; one study declined to participate and one could not locate the primary data.[34,35] Table 1 provides a summary of trials included in the meta-analysis. The trials included 112 953 pregnant women and study-specific sample size ranged from 200[22] to 44 567,[31] with two studies contributing more than two-thirds of total participants.[26,31] Eight trials used the United Nations multiple micronutrient preparation (UNIMMAP; multiple micronutrient supplements formulations in appendix p 1).[20,21,23,26–30] All trials used multiple micronutrient supplements preparations that included at least eight micronutrients in addition to iron-folic acid. The

Clinical Epidemiology Unit, Sitar am Bhartia Institute of Science and Research, New Delhi, India (H P S Sachdev FRCPCH); **UNICEF Regional Office for West and Central Africa, Dakar, Senegal** (N Zagre PhD); **and Department of Epidemiology and Biostatistics, School of Public Health, Xi'an Jiaotong University Health Science Center, Xi'an, Shaanxi Province, China** (L Zeng PhD, Z Zhu MSc)

Correspondence to:
Dr Christopher R Sudfeld, Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston MA 02115, USA
csudfeld@hsph.harvard.edu

See **Online** for appendix

	Location	Years of study	Study design	Participants	Study population
Fawzi,[24] 1998	Dar es Salaam, Tanzania	1995–1997	RCT	1075	HIV-infected pregnant women 12–27 weeks gestation
Christian,[17] 2003	Sarlahi, Nepal	1998–2001	cRCT	4926	Pregnant women
Ramakrishnan,[18] 2003	Cuernavaca, Mexico	1997–2000	RCT	873	Pregnant women <13 weeks gestation
Friis,[19] 2004	Harare, Zimbabwe	1996–1997	RCT	1669	Pregnant women 22–36 weeks gestation including 725 HIV-infected women
Kaestel,[20] 2005	Bissau, Guinea-Bissau	2001–02	RCT	2100	Pregnant women <37 weeks gestation
Osrin,[21] 2005	Dhanusha and Mahottari Districts, Nepal	2002–04	RCT	1200	Singleton pregnant women between 12–20 weeks gestation
Gupta,[22] 2007	East Delhi, India	2002–03	RCT	200	Pregnant women with BMI <18·5 kg/m², 24–32 weeks gestation
Zagre,[23] 2007	Maradi, Niger	2004–06	cRCT	2902	Pregnant women <28 weeks gestation
Fawzi,[25] 2007	Dar es Salaam, Tanzania	2001–04	RCT	8468	HIV-uninfected pregnant women of 12–27 weeks gestation
Shankar,[26] 2008	Lombok island, Indonesia	2001–04	cRCT	31 290	Pregnant women (34% first, 43% second, and 23% third trimester)
Zeng,[27] 2008	Shaanxi Province, China	2002–06	cRCT	3811	Pregnant women (folic acid-only group excluded)
Roberfroid,[28] 2008	Hounde health district, Burkina Faso	2004–06	RCT	1426	Pregnant women
Bhutta,[29] 2009	Bilal colony, Karachi, Kot Diji, Sindh, Pakistan	2002–04	cRCT	2378	Pregnant women <16 weeks gestation
Persson,[30] 2012	Matlab, Bangladesh	2001–03	RCT	4436	Pregnant women between 6–8 weeks gestation
West,[31] 2014	Gaibandha and Rangpur, Bangladesh	2007–12	cRCT	44 567	Pregnant women (79% <13 weeks gestation)
Ashorn,[32] 2015	Mangochi District, Malawi	2011–13	RCT	929	Pregnant women <20 weeks gestation (excluding lipid-based nutrient supplement group)
Adu-Afarwuah,[34] 2015	Somanya-Kpong, Ghana	2009–11	RCT	703	Pregnant women <20 weeks gestation (excluding lipid-based nutrient supplement group)

RCT=randomised control trial. cRCT=cluster randomised control trial.

Table 1: **Characteristics of trials included in the meta-analysis**

prevalence of effect modifiers and cumulative incidence of study outcomes by trial are presented in the appendix (pp 3, 4). All trials were graded low or moderate risk of bias (appendix p 2). Funnel plots did not provide clear evidence of publication bias or small study effects (appendix pp 221–224).

Figure 1 presents subgroup-specific pooled effect sizes for the following outcomes: stillbirth, neonatal mortality, infant mortality, low birthweight, preterm, and small-for-gestational-age births as per the Oken standard. Forest plots for all subgroup meta-analyses are presented in the appendix (pp 5–205). Table 2 presents the effect of maternal multiple micronutrient supplements on stillbirth, neonatal mortality, mortality to 6 months, and infant mortality stratified by potential effect modifiers. We did not identify any factors that significantly modified the effect of multiple micronutrient supplements on stillbirth. In meta-analyses including all livebirths, there was no overall effect of multiple micronutrient supplements on mortality at any timepoint; however, there were several subgroups for which multiple micronutrient supplements provided significant survival benefits. We found sex modified the effect of multiple micronutrient supplements on survival in the early neonatal, neonatal, and infant periods (p values for heterogeneity: 0·047, 0·007, 0·04; table 2; appendix p 23). Multiple micronutrient supplements significantly reduced the risk of neonatal mortality by 15% among females (95% CI 4–25) with a similar magnitude of reduction for early neonatal, 6 months, and infant mortality. Significant mortality benefits of multiple micronutrient supplements for females were also found at all timepoints in random effects sensitivity analyses (appendix p 206). Multiple micronutrient supplements provided significantly greater 6-month mortality reduction among anaemic pregnant women as compared with non-anaemic pregnant women (RR 0·71, 95% CI 0·60–0·86 *vs* 0·93, 0·78–1·11; p value for heterogeneity 0·04). Maternal adherence to the intervention also modified the effect of multiple micronutrient supplements on infant mortality, with survival benefits for infants born to women with higher than 95% adherence to the supplements (table 2). No subgroup had significantly increased risk of stillbirth or neonatal, 6 month, or infant mortality in both fixed and random effects meta-analyses (table 2 and appendix p 206).

Among all livebirths, multiple micronutrient supplements significantly reduced the risk of very low

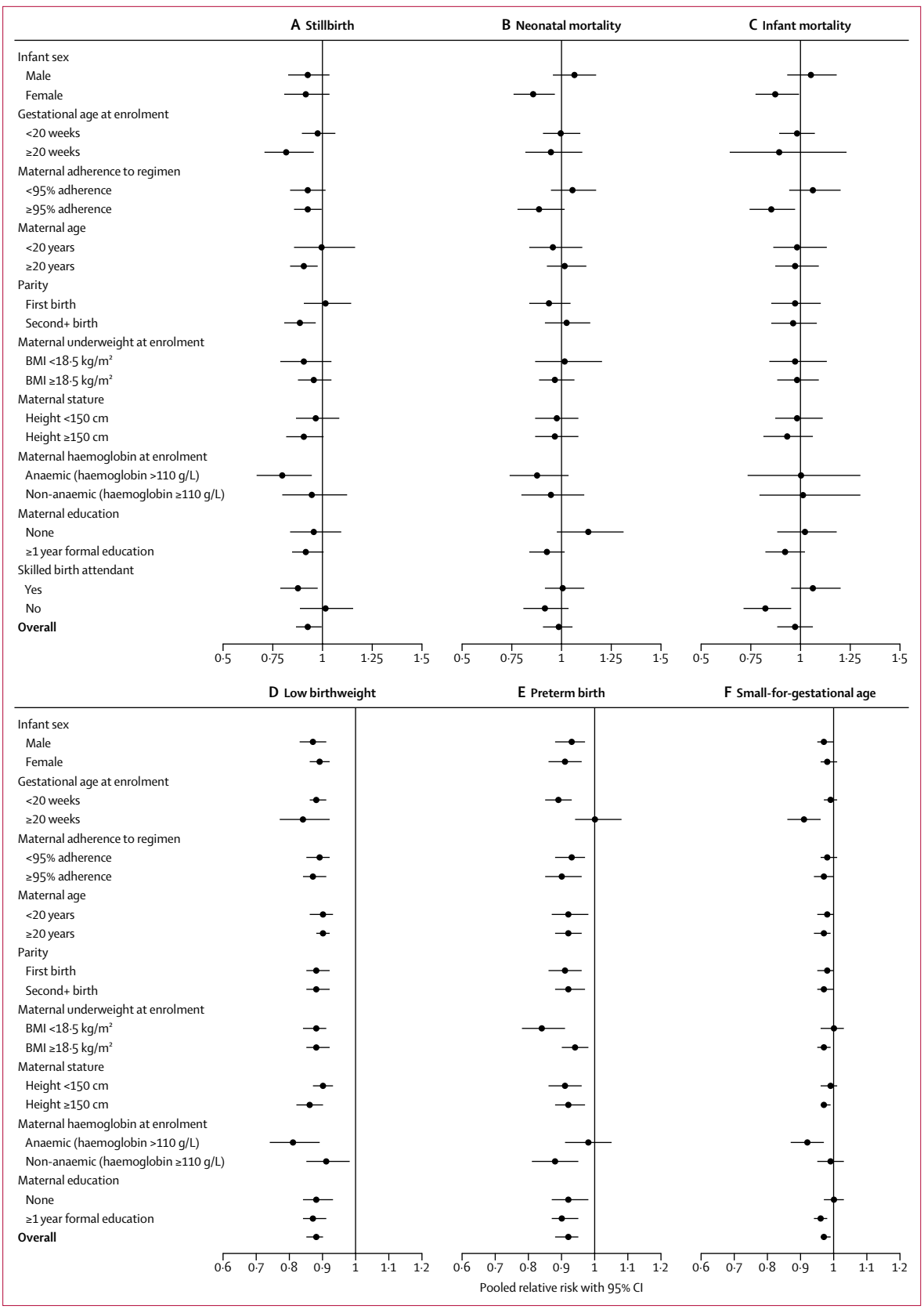

Figure: **The effect of multiple micronutrient supplements containing iron-folic acid compared with iron-folic acid alone on (A) stillbirth, (B) neonatal mortality, (C) infant mortality, (D) low birthweight, (E) preterm birth, and (F) small-for-gestational-age as defined by the Oken standard,[13] stratified by modifiers of interest**

	Stillbirth			Neonatal mortality (≤28 days)			6-month mortality (≤180 days)			Infant mortality (≤365 days)		
	n	Relative risk (95% CI)	p value heterogeneity	n	Relative risk (95% CI)	p value heterogeneity	n	Relative risk (95% CI)	p value heterogeneity	n	Relative risk (95% CI)	p value heterogeneity
Overall, fixed effects	16	0·92 (0·86–0·99)	..	12	0·98 (0·90–1·05)	..	9	0·93 (0·85–1·00)	..	8	0·97 (0·88–1·06)	..
Overall, random effects	16	0·97 (0·85–1·11)	..	12	0·99 (0·89–1·09)	..	9	0·93 (0·86–1·00)	..	8	0·97 (0·88–1·06)	..
Infant sex	16	..	0·88	12	..	0·007	9	..	0·06	8	..	0·04
Male	..	0·92 (0·82–1·03)	..	..	1·06 (0·95–1·17)	..	..	0·98 (0·89–1·09)	..	..	1·05 (0·93–1·18)	..
Female	..	0·91 (0·80–1·03)	..	..	0·85 (0·75–0·96)	..	..	0·85 (0·75–0·95)	..	..	0·87 (0·77–0·99)	..
Gestational age at enrolment	10		0·05	10		0·60	7		0·10	7		0·57
<20 weeks	..	0·97 (0·89–1·06)	..	..	0·99 (0·90–1·09)	..	..	0·96 (0·87–1·05)	..	..	0·98 (0·89–1·07)	..
≥20 weeks	..	0·81 (0·70–0·95)	..	..	0·94 (0·81–1·10)	..	..	0·82 (0·69–0·96)	..	..	0·89 (0·64–1·23)	..
Maternal adherence to regimen	11		0·96	9		0·05	6		0·11	5		0·02
<95% Adherence	..	0·92 (0·83–1·01)	..	..	1·05 (0·94–1·17)	..	..	0·98 (0·88–1·09)	..	..	1·06 (0·94–1·20)	..
≥95% Adherence	..	0·92 (0·85–0·99)	..	..	0·88 (0·77–1·01)	..	..	0·85 (0·74–0·97)	..	..	0·85 (0·74–0·97)	..
Maternal age	16		0·26	9		0·51	8		0·68	8		0·87
< 20 years	..	0·99 (0·85–1·16)	..	..	0·95 (0·83–1·10)	..	..	0·96 (0·84–1·09)	..	..	0·98 (0·86–1·13)	..
≥ 20 years	..	0·90 (0·83–0·97)	..	..	1·01 (0·92–1·12)	..	..	0·92 (0·84–1·02)	..	..	0·97 (0·87–1·09)	..
Parity	15		0·06	12		0·26	9		0·76	8		0·87
First birth	..	1·01 (0·90–1·14)	..	..	0·93 (0·83–1·04)	..	..	0·94 (0·84–1·04)	..	..	0·97 (0·85–1·10)	..
≥ Second birth	..	0·88 (0·80–0·96)	..	..	1·02 (0·91–1·14)	..	..	0·92 (0·82–1·02)	..	..	0·96 (0·85–1·08)	..
Maternal BMI at enrolment	12		0·53	11		0·61	8		0·60	7		0·95
<18·5 kg/m²	..	0·90 (0·78–1·04)	..	..	1·01 (0·86–1·20)	..	..	0·96 (0·83–1·12)	..	..	0·97 (0·84–1·13)	..
≥18·5 kg/m²	..	0·95 (0·87–1·04)	..	..	0·96 (0·88–1·06)	..	..	0·92 (0·84–1·01)	..	..	0·98 (0·88–1·09)	..
Maternal height	14		0·38	10		0·98	7		0·84	6		0·58
<150 cm	..	0·96 (0·86–1·08)	..	..	0·97 (0·86–1·08)	..	..	0·92 (0·83–1·02)	..	..	0·98 (0·87–1·11)	..
≥150 cm	..	0·90 (0·81–1·00)	..	..	0·96 (0·86–1·08)	..	..	0·91 (0·81–1·02)	..	..	0·93 (0·81–1·06)	..
Maternal haemoglobin at enrolment	13		0·16	10		0·54	8		0·04	7		0·95
Anaemic (haemoglobin <110 g/L)	..	0·79 (0·66–0·94)	..	..	0·87 (0·73–1·03)	..	..	0·71 (0·60–0·86)	..	..	1·00 (0·73–1·30)	..
Non-anaemic (haemoglobin ≥110 g/L)	..	0·94 (0·79–1·12)	..	..	0·94 (0·79–1·11)	..	..	0·93 (0·78–1·11)	..	..	1·01 (0·79–1·30)	..
Maternal education	14		0·62	12		0·02	8		0·22	7		0·24
None	..	0·95 (0·83–1·09)	..	..	1·13 (0·97–1·31)	..	..	0·99 (0·86–1·13)	..	..	1·02 (0·88–1·18)	..
≥1 year formal education	..	0·91 (0·84–1·00)	..	..	0·92 (0·83–1·01)	..	..	0·89 (0·81–0·98)	..	..	0·92 (0·82–1·02)	..
Skilled birth attendant	10		0·09	10		0·23	7		0·01	6		0·006
Yes	..	0·87 (0·78–0·97)	..	..	1·00 (0·91–1·11)	..	..	1·00 (0·90–1·11)	..	..	1·06 (0·95–1·20)	..
No	..	1·01 (0·88–1·15)	..	..	0·91 (0·80–1·03)	..	..	0·82 (0·74–0·92)	..	..	0·82 (0·71–0·95)	..

n=number of studies included in subgroup analysis.

Table 2: **The effect of maternal multiple micronutrient supplements on stillbirth, neonatal mortality, mortality to 6 months, and infant mortality, stratified by potential effect modifiers**

birthweight, low birthweight, early preterm, preterm, and small-for-gestational-age births (Oken or Intergrowth standards; table 3 and appendix p 80, p 122). We also found multiple micronutrient supplements significantly increased the risk of being born large-for-gestational-age by the Intergrowth standard (RR 1·11, 95% CI 1·04–1·19; appendix p 150). There was no evidence that infant sex modified the effect of multiple micronutrient supplements

	Low birthweight (<2500 g)			Preterm (<37 weeks)			Small-for-gestational-age*			Large-for-gestational-age*		
	n	Relative risk (95% CI)	p value heterogeneity	n	Relative risk (95% CI)	p value heterogeneity	n	Relative risk (95% CI)	p value heterogeneity	n	Relative risk (95% CI)	p value heterogeneity
Overall, fixed effects	17	0·88 (0·85–0·90)	..	16	0·92 (0·88–0·95)	..	16	0·97 (0·96–0·99)	..	13	1·05 (0·95–1·15)	..
Overall, random effects	17	0·86 (0·81–0·92)	..	16	0·93 (0·87–0·98)	..	16	0·94 (0·90–0·98)	..	13	1·04 (0·92–1·18)	..
Infant sex	17	..	0·48	15	..	0·63	15	..	0·62	12	..	0·18
Male	..	0·87 (0·83–0·91)	..	..	0·93 (0·88–0·97)	..	..	0·97 (0·95–1·00)	..	..	1·11 (0·98–1·25)	..
Female	..	0·89 (0·86–0·92)	..	..	0·91 (0·86–0·96)	..	..	0·98 (0·96–1·01)	..	..	0·98 (0·86–1·12)	..
Gestational age at enrolment	13		0·32	11		0·03	12		0·004	8		0·09
<20 weeks	..	0·88 (0·86–0·91)	..	..	0·89 (0·85–0·93)	..	..	0·99 (0·97–1·01)	..	..	0·99 (0·86–1·13)	..
≥20 weeks	..	0·84 (0·77–0·92)	..	..	1·00 (0·94–1·08)	..	..	0·91 (0·86–0·96)	..	..	1·18 (1·02–1·37)	..
Maternal adherence to regimen	12		0·61	10		0·62	11		0·43	8		0·88
<95% Adherence	..	0·89 (0·85–0·92)	..	..	0·93 (0·88–0·97)	..	..	0·98 (0·96–1·01)	..	..	1·03 (0·90–1·18)	..
≥95% Adherence	..	0·87 (0·84–0·91)	..	..	0·90 (0·85–0·96)	..	..	0·97 (0·94–1·00)	..	..	1·05 (0·90–1·22)	..
Maternal age	15		0·85	15		0·82	16		0·70	11		0·51
<20 years	..	0·90 (0·86–0·93)	..	..	0·92 (0·87–0·98)	..	..	0·98 (0·95–1·00)	..	..	0·98 (0·79–1·22)	..
≥20 years	..	0·90 (0·88–0·92)	..	..	0·92 (0·88–0·96)	..	..	0·97 (0·94–0·99)	..	..	1·06 (0·96–1·18)	..
Parity	16		0·88	14		0·63	15		0·94	10		0·09
First birth	..	0·88 (0·85–0·92)	..	..	0·91 (0·86–0·96)	..	..	0·98 (0·95–1·00)	..	..	0·94 (0·78–1·12)	..
≥ Second birth	..	0·88 (0·85–0·92)	..	..	0·92 (0·88–0·97)	..	..	0·97 (0·95–1·00)	..	..	1·12 (1·00–1·25)	..
Maternal BMI at enrolment	16		0·80	13		0·01	16		0·20	8		0·045
<18·5 kg/m²	..	0·88 (0·84–0·91)	..	..	0·84 (0·78–0·91)	..	..	1·00 (0·96–1·03)	..	..	0·77 (0·57–1·05)	..
≥18·5 kg/m²	..	0·88 (0·85–0·92)	..	..	0·94 (0·90–0·98)	..	..	0·97 (0·95–0·99)	..	..	1·08 (0·97–1·21)	..
Maternal height	16		0·16	15		0·58	16		0·27	10		0·17
<150 cm	..	0·90 (0·87–0·93)	..	..	0·91 (0·86–0·96)	..	..	0·99 (0·96–1·01)	..	..	0·93 (0·78–1·12)	..
≥150 cm	..	0·86 (0·82–0·90)	..	..	0·92 (0·88–0·97)	..	..	0·97 (0·96–0·99)	..	..	1·09 (0·97–1·22)	..
Maternal hemoglobin at enrolment	14		0·049	12		0·05	13		0·03	9		0·09
Anaemic (haemoglobin <110 g/L)	..	0·81 (0·74–0·89)	..	..	0·98 (0·91–1·05)	..	..	0·92 (0·87–0·97)	..	..	1·25 (1·06–1·49)	..
Non-anaemic (haemoglobin ≥110 g/L)	..	0·91 (0·85–0·98)	..	..	0·88 (0·81–0·95)	..	..	0·99 (0·95–1·03)	..	..	0·99 (0·80–1·22)	..
Maternal education	16		0·75	14		0·64	15		0·049	9		0·75
None	..	0·88 (0·84–0·93)	..	..	0·92 (0·87–0·98)	..	..	1·00 (0·97–1·03)	..	..	1·07 (0·88–1·29)	..
≥1 year formal education	..	0·87 (0·84–0·91)	..	..	0·90 (0·87–0·95)	..	..	0·96 (0·94–0·98)	..	..	1·03 (0·92–1·16)	..

n=number of studies included in subgroup analysis. *As defined by the Oken standard.[13]

Table 3: **The effect of maternal multiple micronutrient supplements on low birthweight, preterm birth, small-for-gestational-age birth, and large-for-gestational-age birth, stratified by potential effect modifiers**

on low birthweight, prematurity, or small-for-gestational-age births. Multiple micronutrient supplements had a greater effect on reducing the risk of low birthweight (RR 0·81; 95% CI 0·74–0·89) and small-for-gestational-age by Oken standard (0·92, 0·87–0·97) in anaemic pregnant women versus non-anaemic pregnant women (p values for heterogeneity 0·049 and 0·03, respectively; table 3). Maternal BMI modified the effect of multiple micronutrient supplements on several birth outcomes. Multiple micronutrient supplements reduced the risk of being born early preterm and preterm with greater magnitude among pregnant women with a BMI lower than 18·5 kg/m² compared with non-underweight pregnant women (table 3, appendix p 86). Maternal BMI also modified the risk of having a large-for-gestational-age birth based on the Oken standard (p value for heterogeneity 0·045); with non-underweight women (BMI ≥18·5 kg/m²) having a greater increase in risk of large-for-gestational-age birth (table 4).

Gestational age at multiple micronutrient supplements initiation modified the effect of supplementation. Women initiating multiple micronutrient supplements before 20 weeks gestation had greater reductions in the risk of preterm birth (RR 0·89, 95% CI 0·85–0·93; p value for heterogeneity 0·03; table 3). However, multiple micronutrient supplements provided greater reductions in the risk of small-for-gestational-age birth in women initiating supplementation after 20 weeks (RR 0·91, 95% CI 0·86–0·96; p value heterogeneity 0·004; table 3). Multiple micronutrient supplements initiation before or after 20 weeks gestation conferred similar benefits in reducing the risk of low birthweight (table 3).

As a sensitivity analysis, we stratified studies by whether or not they used the same dose of iron in the multiple micronutrient supplements and iron-folic acid groups. The appendix provides overall estimates (appendix p 208) and subgroup estimates (appendix pp 209–217) of the effect of multiple micronutrient supplements for trials using the same dose of iron in the multiple micronutrient supplements and iron-folic acid alone groups versus trials using a lower dose iron in the multiple micronutrient supplements group than the iron-folic acid alone group (all used ≤30 mg iron for multiple micronutrient supplements and 60 mg iron for iron-folic acid alone). Among trials using the same dose of iron in both groups, the benefits of multiple micronutrient supplements were consistent with the primary analysis. By contrast, some subgroups given multiple micronutrient supplements with low dose iron (≤30 mg) had higher stillbirth and neonatal mortality than iron-folic acid alone with 60 mg iron. Specifically, multiple micronutrient supplements containing a lower dose of iron than the iron-folic acid comparison group were associated with an increased stillbirth rate among first pregnancies, early neonatal mortality in women who initiated supplementation before 20 weeks gestation, early neonatal and neonatal mortality in women with <95% adherence, and early neonatal mortality for multigravidae.

Discussion

Our findings show that pregnant women who take antenatal multiple micronutrient supplements including iron-folic acid have a lower risk of having a baby with low birthweight, a preterm birth, or having a small-for-gestational-age baby. Furthermore, we identified several factors that modified the effect of multiple micronutrient supplements on infant survival and birth outcomes.

The effect of multiple micronutrient supplements on survival was modified by infant sex. Multiple micronutrient supplements consistently reduced mortality by about 15% in females during the first year of life, but we did not record significant benefits in males. The biological mechanisms leading to these sex differences are not clear. West and colleagues[31] and Lee and colleagues[36] have previously proposed that sex differences in the mortality effect of multiple micronutrient supplements could be explained by differences in birth size by sex. Males have greater length, head circumference, and birthweight on average than females, and increased birth size due to multiple micronutrient supplements might lead to greater birth complications in males.[37] However, we noted no sex differences in the effect of multiple micronutrient supplements on stillbirth, which suggests that effect modification by sex might operate through other mechanisms or vary with the population context. The burden of infections and leading causes of mortality have been shown to vary by infant sex;[38,39] additional information about the causes and timing of deaths within trials might help clarify why multiple micronutrient supplements seem to be more beneficial for female infants. Nevertheless, we do not recommend programmes considering implementation of multiple micronutrient supplements target only pregnant women carrying female fetuses as both male and female neonates experience birthweight benefits and small positive survival benefits are possible in males.

Multiple micronutrient supplements had a bigger effect on birth outcomes in women with poor nutritional status, as indicated by anaemia or low BMI, at the start of supplementation, as initially reported in the SUMMIT study.[26] Anaemic women had greater reductions in the risk of low birthweight, small-for-gestational-age birth, and mortality to 6 months than non-anaemic pregnant women. The effect of multiple micronutrient supplements on preterm birth was also greater for pregnant women who had a BMI of lower than 18·5 kg/m² at the start of supplementation. These findings suggest that iron-folic acid alone is likely an insufficient intervention for anaemic pregnant women and justifies continued focus on anaemia and low BMI as key effect modifiers for nutrition interventions in pregnancy. A recent multiple micronutrient supplements trial[34] done in China among non-anaemic and mildly anaemic women (not included in our meta-analysis) found no effect of multiple micronutrient supplements on perinatal mortality and a non-significant 10% reduction in low birthweight. These

findings are consistent with our non-anaemic subgroup results, which showed no effect of multiple micronutrient supplements on early neonatal, neonatal, or infant mortality and an 8% reduction in low birthweight.

Due to the clustering of protein-energy and micronutrient deficiencies, we cannot directly examine whether improvement in maternal haemoglobin status mediated a greater effect of multiple micronutrient supplements on low birthweight in anaemic women. Anaemia might be a proxy for deficiencies of micronutrients included in multiple micronutrient supplements, as well as numerous other factors including maternal infection.[40,41] Findings of a previous meta-analysis showed that multiple micronutrient supplements (which included iron) had a similar effect on haemoglobin and anaemia than iron alone or iron with folic acid.[42] Notably, some trials included in our meta-analysis and the anaemia meta-analysis used higher dose iron in the control group than the multiple micronutrient supplements arm, which might have attenuated the haemoglobin, mortality, and birth outcome effects of multiple micronutrient supplements, particularly in anaemic pregnant women.[20,21,27–29,32,33,35,42] Despite this, we still find a larger effect of multiple micronutrient supplements among anaemic than for non-anaemic pregnant women. There are several haemoglobin independent pathways by which multiple micronutrient supplements might improve birth outcomes,[5] including reductions in maternal and fetal inflammation,[43] improvements in oxidative metabolism and placental function,[44,45] and altered maternal endocrine effects.[46] Although the biological mechanisms through which multiple micronutrient supplements provides benefits are unclear, our meta-analysis indicates that the population-level benefits for birth outcomes are likely to be greater in settings with high rates of maternal nutritional deficiencies. It is also important to note that in the MINIMat trial women who received both early food supplementation and multiple micronutrient supplements had the lowest rate of infant mortality;[30] combined macronutrient and micronutrient interventions might produce even greater effects in settings with high rates of maternal malnutrition.

We did not identify any subgroup that experienced significantly elevated risk of stillbirth or mortality at any timepoint in the primary analysis. Multiple micronutrient supplements trial reports have raised concerns that increased birth size due to multiple micronutrient supplements may increase the risk of cephalopelvic disproportion and neonatal asphyxia, particularly among women of small stature.[17,31] We found that multiple micronutrient supplements indeed increased the risk of large-for-gestational-age births (as defined by the Intergrowth standard[14]), which could hypothetically increase the risk of maternal-fetal disproportion and related birth complications. However, we found no indication that mothers who took multiple micronutrient supplements and whose height was less than 150 cm had increased risk of stillbirth or mortality at any timepoint. As such, alternative interpretations or mechanisms to explain no overall effect of multiple micronutrient supplements on mortality should be explored.

We also provide evidence that iron dosage influences the observed effect of multiple micronutrient supplements on stillbirth and mortality. Specifically, the sensitivity analyses revealed benefits and no significant harmful effects overall or in any subgroup among trials that used the same dose of iron in the multiple micronutrient supplements and iron-folic acid alone arms. By contrast, the sensitivity analyses also found that multiple micronutrient supplements with low dose iron (<30 mg) results in a higher observed stillbirth and mortality in some subgroups when compared to iron-folic acid alone with 60 mg iron. The most recent Cochrane Review found similar effect modification by iron dose on perinatal mortality.[6] Furthermore, the WHO antenatal care guidelines noted the potential for harmful effects of multiple micronutrient supplements on neonatal mortality among a subgroup analysis in which 5 out of 6 trials used low dose iron (≤30 mg) in the multiple micronutrient supplements group and 60 mg iron in the iron-folic acid alone group.[10] Taken together with previous analyses, our data suggest that both iron and multiple micronutrients have beneficial effects and that multiple micronutrients together with iron-folic acid provide even greater benefits than iron-folic acid alone. Accordingly, countries and programmes considering implementation of multiple micronutrient supplements should use a formulation with an iron dose similar to what they currently use; for example, multiple micronutrient supplements that contains 60 mg iron should be considered in settings where 60 mg iron-folic acid is currently implemented.

Notwithstanding the large sample size and consistency of our findings, there are several limitations to our meta-analysis. First, because of the number of subgroup analyses we did, there is an increased risk of type 1 errors inherent to the number of heterogeneity tests presented. However, our findings as a whole exceed those that would be expected by chance; 13 of 70 tests for heterogeneity for mortality outcomes were significant (probability of occurring by chance alone <0·01%). There is also low probability of finding 26 of 146 subgroups had significant survival benefits (<0·01%) and that no subgroups had increased mortality risk (2·5%) if we construct a hypothesis assuming there was no true effect of multiple micronutrient supplements on mortality in any subgroup. Second, as previously discussed, some trials used a higher dose of iron in the control group as compared with the multiple micronutrient supplements group, and our sensitivity analysis suggests that inclusion of these trials resulted in attenuation of the effect of multiple micronutrient supplementation because the iron-folic acid alone group

participants might have experienced benefits from additional iron.[20,21,27–29,32,33] Third, the JiVitA-3[31] and SUMMIT[26] trials are weighted heavily in many of the subgroup strata because of their large sample sizes and high event rates. Our sensitivity analyses show that sex differences in the effect of multiple micronutrient supplements on neonatal mortality are robust to excluding either of these studies (appendix pp 218–220). However, the stronger benefit of multiple micronutrient supplements on 6-month mortality in infants born to anaemic women is driven by the SUMMIT study,[26] and the stronger benefit of multiple micronutrient supplements on preterm birth among infants born to underweight women and infant mortality among male infants, are driven by JiVitA-3[31] (appendix pp 218–220). Fourth, we were unable to examine HIV as a potential effect modifier since only two trials included both HIV-infected and HIV-uninfected women. Nevertheless, there was no indication that the effect of multiple micronutrient supplements varied by maternal HIV status in these studies.[19,32] Finally, although our analysis identified several maternal and child factors that alter the effect of multiple micronutrient supplements on mortality and birth outcomes, we can provide only limited insight into the biological mechanisms through which multiple micronutrient supplements may operate. As poor socioeconomic status, significant barriers to health services, and nutritional deficiencies often coexist, the effect modifiers we examined in this analysis (eg, skilled birth attendants, maternal underweight, and maternal anaemia) have overlap as indicators of underlying adversity. Even so, the factors identified in this paper suggest subgroups that might experience the greatest benefits from multiple micronutrient supplements, irrespective of the mechanisms through which multiple micronutrient supplements operates.

Our findings established that multiple micronutrient supplements reduced mortality in female neonates, and although multiple micronutrient supplements increased birthweight and reduced preterm among all infants, the greatest effects were for those born to pregnant women with nutritional deficiency as indicated by anaemia or low BMI. Based on the included data and methods of this study, we also found none of the 26 subgroups, or the population overall, showed multiple micronutrient supplements significantly increased the risk of stillbirth or neonatal, six-month, or infant mortality. A systematic review[47] that assessed the long-term health effects noted no significant evidence that multiple micronutrient supplements improved child growth, body composition, blood pressure, respiratory, or cognitive outcomes as compared with iron folic-acid alone. However, a recently published long-term follow-up study[48] of SUMMIT found that multiple micronutrient supplements significantly improved procedural memory and produced better scores on 18 of 21 cognitive tests among Indonesian children aged 9–12 years.

This new evidence suggests that WHO should consider re-evaluating the balance of benefits and harms of universal multiple micronutrient supplements in their antenatal care recommendations. Programmes and low-income and middle-income countries considering implementation of multiple micronutrient supplements have the opportunity to simultaneously expand coverage of early antenatal care attendance and multiple micronutrient supplements including iron-folic acid, while also improving the quality of antenatal care counselling and services to produce population-level infant health benefits, which might be greater than any of these strategies in isolation. Packaging multiple micronutrient supplements with effective antenatal care interventions for coordinated delivery is consistent with the Sustainable Development Goals, which emphasise the identification of intervention synergies that have the potential for rapid impact.[49]

Contributors

ERS, CRS, AHS, and WWF designed the study (project conception, development of overall research plan, and study oversight). All authors contributed input and reviewed the study protocol and assisted or completed statistical analyses for their respective trials. ERS, LS-FW, and CRS developed statistical programme code for trial-specific analyses. ERS and CRS pooled the data and did the meta-analyses. ERS and CRS drafted the initial paper and have primary responsibility for final content. All authors reviewed and contributed to the final manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

We would like to acknowledge Alain B Labrique, Saijuddin Shaikh, Subarna K. Khatry, Steven L. LeClerq, Peter Aaby, Anna Lartey, Harriet E Okronipa, Dharma S Manandhar, Anthony Costello, Victor M Aguayo, Lynnette M Neufeld, Rajeev Kumar Malhotra, Susy Sebayang, Mandri Apriatni, Hong Yan, Michael J Dibley, Mily Ray, and Gwenola Desplats for their contributions to the parent trials.

References

1 WHO. Vitamin and mineral requirements in human nutrition. Geneva: World Health Organziation, 2004.
2 King JC. Physiology of pregnancy and nutrient metabolism. *Am J Clin Nutr* 2000; **71:** 1218–25.
3 Black RE. Micronutrients in pregnancy. *Br J Nutr* 2001; **85** (suppl 2)**:** S193–97.
4 Haider BA, Olofin I, Wang M, Spiegelman D, Ezzati M, Fawzi WW. Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis. *BMJ* 2013; **346**: f3443
5 Gernand AD, Schulze KJ, Stewart CP, West KP Jr, Christian P. Micronutrient deficiencies in pregnancy worldwide: health effects and prevention. *Nat Rev Endocrinol* 2016; **12**: 274–89.
6 Haider BA, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database Syst Rev* 2017; **4**: CD004905.
7 West KP, Katz J, Khatry SK, et al. Double blind, cluster randomised trial of low dose supplementation with vitamin A or beta carotene on mortality related to pregnancy in Nepal. The NNIPS-2 Study Group. *BMJ* 1999; **318:** 570–75.
8 Christian P, Labrique AB, Ali H, et al. Maternal vitamin A and beta-carotene supplementation and risk of bacterial vaginosis: a randomized controlled trial in rural Bangladesh. *Am J Clin Nutr* 2011; **94:** 1643–49.
9 Fall CH, Fisher DJ, Osmond C, Margetts BM, Maternal Micronutrient Supplementation Study G. Multiple micronutrient supplementation during pregnancy in low-income countries: a meta-analysis of effects on birth size and length of gestation. *Food Nutr Bull* 2009; **30** (suppl 4)**:** S533–46.

10 WHO. WHO recommendations on antenatal care for a positive pregnancy experience. Geneva, Switzerland: World Health Organization, 2016.

11 Kawai K, Spiegelman D, Shankar AH, Fawzi WW. Maternal multiple micronutrient supplementation and pregnancy outcomes in developing countries: meta-analysis and meta-regression. *Bull World Health Organ* 2011; **89:** 402–11.

12 Fall CH, Fisher DJ, Osmond C, Margetts BM. Multiple micronutrient supplementation during pregnancy in low-income countries: a meta-analysis of effects on birth size and length of gestation. *Food Nutr Bull* 2009; **30** (suppl 4)**:** S533–S46.

13 Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. *BMC Pediat* 2003; **3:** 6.

14 Villar J, Ismail LC, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21 st Project. *Lancet* 2014; **384:** 857–68.

15 Boschi-Pinto C, Young M, Black RE. The Child Health Epidemiology Reference Group reviews of the effectiveness of interventions to reduce maternal, neonatal and child mortality. *Int J Epidemiol* 2010; **39** (suppl 1)**:** i3–6.

16 Steichen T. METANINF: Stata module to evaluate influence of a single study in meta-analysis estimation. *Statistical Software Components* 2001.

17 Christian P, Khatry SK, Katz J, et al. Effects of alternative maternal micronutrient supplements on low birth weight in rural Nepal: double blind randomised community trial. *BMJ* 2003; **326:** 571.

18 Ramakrishnan U, Gonzalez-Cossio T, Neufeld LM, Rivera J, Martorell R. Multiple micronutrient supplementation during pregnancy does not lead to greater infant birth size than does iron-only supplementation: a randomized controlled trial in a semirural community in Mexico. *Am J Clin Nutr* 2003; **77:** 720–25.

19 Friis H, Gomo E, Nyazema N, et al. Effect of multimicronutrient supplementation on gestational length and birth size: a randomized, placebo-controlled, double-blind effectiveness trial in Zimbabwe. *Am J Clin Nutr* 2004; **80:** 178–84.

20 Kaestel P, Michaelsen KF, Aaby P, Friis H. Effects of prenatal multimicronutrient supplements on birth weight and perinatal mortality: a randomised, controlled trial in Guinea-Bissau. *Eur J Clin Nutr* 2005; **59:** 1081–89.

21 Osrin D, Vaidya A, Shrestha Y, et al. Effects of antenatal multiple micronutrient supplementation on birthweight and gestational duration in Nepal: double-blind, randomised controlled trial. *Lancet* 2005; **365:** 955–62.

22 Gupta P, Ray M, Dua T, Radhakrishnan G, Kumar R, Sachdev HP. Multimicronutrient supplementation for undernourished pregnant women and the birth size of their offspring: a double-blind, randomized, placebo-controlled trial. *Arch Pediatr Adolesc Med* 2007; **161:** 58–64.

23 Zagre NM, Desplats G, Adou P, Mamadoultaibou A, Aguayo VM. Prenatal multiple micronutrient supplementation has greater impact on birthweight than supplementation with iron and folic acid: a cluster-randomized, double-blind, controlled programmatic study in rural Niger. *Food Nutr Bull* 2007; **28:** 317–27.

24 Fawzi WW, Msamanga GI, Spiegelman D, et al. Randomised trial of effects of vitamin supplements on pregnancy outcomes and T cell counts in HIV-1-infected women in Tanzania. *Lancet* 1998; **351:** 1477–82.

25 Fawzi WW, Msamanga GI, Urassa W, et al. Vitamins and perinatal outcomes among HIV-negative women in Tanzania. *N Engl J Med* 2007; **356:** 1423–31.

26 Supplementation with Multiple Micronutrients Intervention Trial Study Group, Shankar AH, Jahari AB, et al. Effect of maternal multiple micronutrient supplementation on fetal loss and infant death in Indonesia: a double-blind cluster-randomised trial. *Lancet* 2008; **371:** 215–27.

27 Zeng L, Dibley MJ, Cheng Y, et al. Impact of micronutrient supplementation during pregnancy on birth weight, duration of gestation, and perinatal mortality in rural western China: double blind cluster randomised controlled trial. *BMJ* 2008; **337:** a2001.

28 Roberfroid D, Huybregts L, Lanou H, et al. Effects of maternal multiple micronutrient supplementation on fetal growth: a double-blind randomized controlled trial in rural Burkina Faso. *Am J Clin Nutr* 2008; **88:** 1330–40.

29 Bhutta ZA, Rizvi A, Raza F, et al. A comparative evaluation of multiple micronutrient and iron-folic acid supplementation during pregnancy in Pakistan: impact on pregnancy outcomes. *Food Nutr Bull* 2009; **30** (suppl 4)**:** S496–505.

30 Persson LA, Arifeen S, Ekstrom EC, et al. Effects of prenatal micronutrient and early food supplementation on maternal hemoglobin, birth weight, and infant mortality among children in Bangladesh: the MINIMat randomized trial. *JAMA* 2012; **307:** 2050–59.

31 West KP Jr, Shamim AA, Mehra S, et al. Effect of maternal multiple micronutrient vs iron-folic acid supplementation on infant mortality and adverse birth outcomes in rural Bangladesh: the JiVitA-3 randomized trial. *JAMA* 2014; **312:** 2649–58.

32 Ashorn P, Alho L, Ashorn U, et al. The impact of lipid-based nutrient supplement provision to pregnant women on newborn size in rural Malawi: a randomized controlled trial. *Am J Clin Nutr* 2015; **101:** 387–97.

33 Adu-Afarwuah S, Lartey A, Okronipa H, et al. Lipid-based nutrient supplement increases the birth size of infants of primiparous women in Ghana. *Am J Clin Nutr* 2015: **101:** 835–46.

34 Liu JM, Mei Z, Ye R, Serdula MK, Ren A, Cogswell ME. Micronutrient supplementation and pregnancy outcomes: double-blind randomized controlled trial in China. *JAMA Intern Med* 2013; **173:** 276–82.

35 Sunawang, Utomo B, Hidayat A, Kusharisupeni, Subarkah. Preventing low birthweight through maternal multiple micronutrient supplementation: a cluster-randomized, controlled trial in Indramayu, West Java. *Food Nutr Bull* 2009; **30** (suppl 4)**:** S488–S95.

36 Lee AC, Darmstadt GL, Khatry SK, LeClerq SC, Shrestha SR, Christian P. Maternal-fetal disproportion and birth asphyxia in rural Sarlahi, Nepal. *Arch Pediatr Adolesc Med* 2009; **163:** 616–23.

37 Hindmarsh PC, Geary MPP, Rodeck CH, Kingdom JCP, Cole TJ. Intrauterine growth and its relationship to size and shape at birth. *Pediatric Research* 2002; **52:** 263–68.

38 Lawn JE, Blencowe H, Darmstadt GL, Bhutta ZA. Beyond newborn survival: the world you are born into determines your risk of disability-free survival. *Pediatr Res* 2013; **74** (suppl 1)**:** 1–3.

39 Seale AC, Blencowe H, Zaidi A, et al. Neonatal severe bacterial infection impairment estimates in South Asia, sub-Saharan Africa, and Latin America for 2010. *Pediatr Res* 2013; **74** (suppl 1)**:** 73–85.

40 Christian P. Micronutrients and reproductive health issues: an international perspective. *J Nutr* 2003; **133:** 1969S–73S.

41 Jiang T, Christian P, Khatry SK, Wu L, West KP. Micronutrient deficiencies in early pregnancy are common, concurrent, and vary by season among rural Nepali pregnant women. *J Nutr* 2005; **135:** 1106–12.

42 Allen LH, Peerson JM, Maternal Micronutrient Supplementation Study G. Impact of multiple micronutrient versus iron-folic acid supplements on maternal anemia and micronutrient status in pregnancy. *Food Nutr Bull* 2009; **30** (suppl 4)**:** S527–32.

43 Romero R, Chaiworapongsa T, Espinoza J. Micronutrients and intrauterine infection, preterm birth and the fetal inflammatory response syndrome. *J Nutr* 2003; **133** (suppl 2)**:** 1668S–73S.

44 Mistry HD, Williams PJ. The importance of antioxidant micronutrients in pregnancy. *Oxid Med Cell Longev* 2011; **2011:** 841749.

45 Poston L, Igosheva N, Mistry HD, et al. Role of oxidative stress and antioxidant supplementation in pregnancy disorders. *Am J Clin Nutr* 2011; **94** (suppl 6)**:** 1980S–5S.

46 Berti C, Biesalski HK, Gartner R, et al. Micronutrients in pregnancy: current knowledge and unresolved questions. *Clin Nutr* 2011; **30:** 689–701.

47 Devakumar D, Fall CH, Sachdev HS, et al. Maternal antenatal multiple micronutrient supplementation for long-term health benefits in children: a systematic review and meta-analysis. *BMC Med* 2016; **14**: 90.

48 Prado EL, Sebayang SK, Apriatni M, et al. Maternal multiple micronutrient supplementation and other biomedical and socioenvironmental infl uences on children's cognition at age 9–12 years in Indonesia: follow-up of the SUMMIT randomised trial. *Lancet Glob Health* 2017; **5:** e217–28.

49 UN General Assembly. Transforming our world: the 2030 Agenda for Sustainable Development. New York: United Nations, 2015.